PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32811A/HO 67	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/14263	International filing date *(day/month/year)* 15.12.2003	Priority date *(day/month/year)* 16.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D471/04		
Applicant NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.06.2004	21.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8931

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/14263

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-28 as originally filed

Claims, Numbers

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the opinion

The application is directed to

(i) 1,7-naphthyridines (I) (claims 1-7),
(ii) the first medical use of compounds (I) (claim 8),
(iii) the corresponding pharmaceutical composition (claim 9),
(iv) the second medical use of compounds (I) (claims 10-12), and
(v) a process for preparing compounds (I) (claim 13).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 98/18796 A, 07.05.1998.
D2: Hersperger, R. *et al. J. Med. Chem.* **2000**, *43*, 675-682.
D3: EP-A-0 005 232, 14.11.1979.

2 Novelty

D1 relates to 8-aryl-1,7-naphthyridines as PDE4 inhibitors, which generally comprise already the present compounds (I) (cf. claim 1; and page 1, paragraphs 2 and 3). The document, however, does not specifically disclose the present 6-nitrogen-heterocyclyl substituted compounds (I). Consequently, the present claimed matter may be seen as a novel selection from **D1**, with the 6-NR^2R^3-substituent of the compounds (I) as novel technical feature.

D2, similarly, relates to 6,8-disubstituted 1,7-naphthyridines as PDE4 inhibitors. The present compounds (I) differ from those of D2 through the NR^2R^3 group in position 6. The present claimed matter is thus novel vis-à-vis D2.

D3 discloses inter alia psychotropic 1-aryl-3-N-heterocyclyl-isoquinolines. The document is not relevant to the question of novelty of the application, because it does

not relate to naphthyridines.

In view of **D1** to **D3** the application complies with the criterion of novelty according to Article 33(2) PCT.

3 Inventive Step

The application describes the synthesis of certain compounds (I) and shows that such compounds (I) exhibit PDE4 inhibitory activity (page 9, last paragraph), which makes them potentially useful in the treatment of inflammatory conditions alike the compounds of **D1**. Starting from **D1** as most relevant state of the art, the problem underlying the application is seen in the provision of further 1,7-naphthyridines of the desired activity. The present compounds (I) are already generally comprised within the teaching of **D1** and, therefore, represent merely an obvious solution of the problem underlying the application. In the absence of any substantiated unexpected effect(s) of the claimed compounds in comparison of the closest related compounds of **D1** (e.g. the hydrochloride of the compound (I) with R^1 = 3-nitrophenyl and NR^2R^3 = 2-oxoaziridine versus example 5 of D1) no inventive activity is seen in the claimed matter. Hence, the claims 1-13 do, at present, not comply with Article 33(3) PCT.

4 Further Deficiencies of the Application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.